REMARKS

Status of the Claims

Claims 1-29 are pending. Claims 1-10, 13-24, and 27-29 are rejected. Claims 11, 12, 25, and 26 are objected to. Claims 1 and 16 have been amended. Claims 1-29 remain pending.

Amendments to the Claims

Claims 1 and 16 have been amended. Specifically, claims 1 and 16 have been amended to recite "said first and said second block of RNA residues are about 3 nucleotides to about 20 nucleotides in length and are contiguous with and flank a block of DNA residues." Support for the length of the RNA blocks can be found, for example, on page 8, lines 1-2 of the specification. Support for the RNA and DNA blocks being "contiguous" can be found throughout the specification, for example, on page 7, lines 29-33, page 9, lines 1-4, and in figures 1-13.

Claims 1 and 16 have been further amended to recite that the first block of DNA residues is "about 5 nucleotides to about 60 nucleotides in length." Support for this amendment can be found, for example, on page 8, lines 16-18 of the specification.

Claims 1 and 16 have been amended to recite that "said DNA block and said second RNA block are identical to a contiguous sequence of the nucleic acid molecule except for the presence of said mismatch in said DNA block." Support for this amendment can be found, for example, on page 10, lines 8-11 of the specification and page 8, lines 7-19.

Claims 1 and 16 have been amended to recite that "said oligonucleotide comprises additional DNA residues that are capable of forming a duplex structure with said first block of RNA residues, said block of DNA residues, and said second block of RNA residues." Support for this amendment can be found, for example on page 7, lines 29-31 and page 8, lines 26-28 of the specification.

The Finality of the Office Action Should Be Withdrawn

A new ground of rejection was issued in the Final Office Action mailed September 23, 2003. Applicants provide below an outline of the prosecution history that demonstrates the new ground of rejection.

The Office Action mailed March 26, 2003, rejected claims 1-10, 13-24, and 27-29 under 35 U.S.C. §112, second paragraph, for indefiniteness. The Office Action states "It is unclear in claims 1 and 16, lines 7-8, how the blocks of the RNA residues can be homologous to the nucleic acid molecule." (page 5, paragraph 4).

The Amendment and Response filed July 28, 2003 addressed the 2nd paragraph rejection by pointing to description in the specification that explains the design of the oligonucleotides and clarifying that upon review of the disclosure in the specification and the Figures, one of skill in the art would clearly understand the structure of the chimeric oligonucleotides recited in the claims.

The Final Office Action of September 23, 2003 continues to maintain the §112, second paragraph, rejection, however, the Examiner raises the following issues: 1) the lengths of the DNA and RNA blocks are unclear; 2) it is unclear if the DNA and RNA blocks are contiguous; and, 3) the duplex structure of the oligonucleotide can not be discerned by the claim language. The Examiner did not previously raise these rejections. Accordingly, the rejection of claims 1-10, 13-24, and 27-29 under 35 U.S.C. §112, second paragraph, that appears in the Final Office Action of September 23, 2003 constitutes a new ground of rejection, and the Examiner is respectfully requested to withdraw finality.

The Rejection of the Claims Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 1-10, 13-24, and 27-29 were rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. This rejection is respectfully traversed.

The Examiner concludes that the duplex structure of the chimeric oligonucleotides recited in independent claims 1 and 16 cannot be discerned from the language of the claims. Independent claims 1 and 16 have been amended to recite that the chimeric "oligonucleotide comprises additional DNA residues that are capable of forming a duplex structure with said first block of RNA residues, said block of DNA residues, and said second block of RNA residues." As amended, the duplex structure of the recited oligonucleotide is clear.

The Examiner also concluded independent claims 1 and 16 were indefinite for not reciting the lengths of the RNA and DNA blocks recited in the claims. To expedite prosecution,

claims 1 and 16 have been amended to recite the length of these various blocks. Specifically, the claims now recite that the "first and said second blocks of RNA residues are about 3 nucleotides to about 20 nucleotides in length" and the "block of DNA residues is about 5 nucleotides to about 60 nucleotides in length." As amended, the length of the recited RNA and DNA blocks is clear.

The Examiner further states that it is unclear if the first and the second RNA blocks are contiguous with the DNA block. Claim 1 and 16 has been amended to clarify that the first and the second block of RNA residues are "contiguous with" and flank a first block of DNA residues.

Claims 1-10, 13-24, and 27-29 have been amended as suggested by the Examiner. Applicants submit claims 1-10, 13-24 and 27-29 satisfy the requirements of 35 U.S.C. §112, second paragraph and, the Examiner is respectfully requested to withdraw the rejection of the claims.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

Written Description

Claims 1-10, 13-24, and 27-29 were rejected under 35 U.S.C. §112, first paragraph, for lack of written description. This rejection is respectfully traversed.

Prior to addressing the Examiner's concerns regarding the sufficient written description for the claimed method, Applicant would like to clarify on the record comments appearing on page 4, lines 1-6 of the September 23, 2003 Office Action. Specifically, the Office Action summarizes the claims of the present application and repeatedly references that the oligonucleotide is designed to target nucleotide sequences that can confer herbicide resistance in a plant. Applicants clarify that independent claims 1 and 16 presently under exam recite inactivating any nucleotide sequence of interest.

The Examiner continues to maintain that claims 1-10, 13-24, and 27-29 lack sufficient written description and concludes that the claims do not indicate which distinguishing attributes

are shared among the members of the genus comprising the recited chimeric oligonucleotides. As previously made of record in the Amendment and Response filed July 28, 2003, ample structure and function is shared among members of the genus to demonstrate possession of the recited chimeric oligonucleotide. The Amendment and Response outlined in detail the specific common attributes shared among the members of the genus including: 1) the spatial relationship of the DNA and RNA blocks; 2) the structure of the RNA blocks shared by members of the genus (i.e., homology with the nucleic acid molecule comprising the nucleotide sequence of interest); 3) the common structure of the DNA blocks shared by members of the genus; and, 4) the common function of the recited chimeric oligonucleotides.

While Applicants maintain claims 1-10, 13-24, and 27-29 satisfied §112, first paragraph, for the reasons previously made of record, to expedite prosecution Applicant's have amended the claims in view of Examiner's comments and submit the requirement under 35 U.S.C. §112, first paragraph, for written description has been satisfied. First, with regard to the common spatial relationship of the DNA and RNA blocks in the chimeric oligonucleotide recited in claims 1 and 16, the Examiner acknowledges the presence of the common spatial relationship but further notes that the length of the RNA and DNA blocks are highly variable and requests clarification as to whether the RNA and DNA blocks are contiguous (Office Action mailed September 23, 2003, page 5, paragraph 1). Claims 1 and 16 have been amended and recite that the first the second blocks of RNA residues are "about 3 nucleotides to about 20 nucleotides in length"; the first block of DNA residues is "about 5 nucleotides to about 60 nucleotides in length"; and, the said first and said second blocks of RNA residues are "contiguous with and flank" the block of DNA residues. As amended, the position of each of the recited "blocks" in the chimeric oligonucleotide and the their respective lengths is clear and thus a clear common spatial relationship exists between the RNA and DNA blocks recited in the claims.

Second, with regard to the common structure within the RNA blocks and within the DNA blocks of the chimeric oligonucleotide recited in claims 1 and 16, the Examiner acknowledges the presence of the common structure of the RNA blocks and the DNA blocks, but further notes that the length of the RNA and DNA blocks in the recited oligonucleotides vary in length and also it is unclear if the RNA and DNA blocks are contiguous (Office Action mailed September

23, 2003, page 5, paragraph 3). As discussed above, claims 1 and 16 have been amended to recite that the approximate length of the RNA and DNA blocks and further recite that the blocks are contiguous. As amended, the Examiner's concern regarding a sufficient common structure of the RNA blocks and the DNA blocks has been addressed.

The Examiner further concludes that the claims encompass "non-contiguous blocks of nucleotides that target different portions of a target gene sequence" (Office Action mailed September 23, 2003, page 6, lines 6-9). While the claims clearly recite functional language stating that 'the chimeric oligonucleotides are capable of recognizing and implementing a nucleotide conversion in said nucleic acid molecule" and, moreover, the specification provides a clear description of the oligonucleotide structure to achieve this function, to expedite prosecution, claims 1 and 16 have been amended to recite "said first RNA block, said DNA block and said second RNA block are identical to a contiguous sequence of the nucleic acid molecule except for the presence of said mismatch in said DNA block." As amended, the structure of the chimeric oligonucleotide is clear.

Sufficient written description requires simply the knowledge and level of skill in the art to permit one of skill to immediately envision the product claimed from the disclosure. *Purdue Pharm L.P. v. Faulding In.*, 596 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("One skilled in the art must immediately discern the limitations at issue in the claims."). As previously made of record, ample structure and function is shared among members of the genus to demonstrate possession of the recited chimeric oligonucleotides. Accordingly, claims 1-10, 13-24, and 27-29 satisfy the requirements of 35 U.S.C. §112, first paragraph, and the Examiner is respectfully requested to withdraw the rejection.

Enablement

Claims 1-8, 13-22, and 27-29 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. This rejection is respectfully traversed.

The Examiner's conclusions are based on three lines of reasoning: 1) the length of the oligonucleotide is variable; 2) the identification of nucleotide mismatches in any and/or all target genes of interest that would convert these target genes to inactive forms in undue; and, 3)

the unpredictability of the method in view of data presented in the specification. Each of the Examiner's concerns regarding the enablement of claims 1-8, 13-22, and 27-29 are addressed below.

I. Regarding the variable length of the oligonucleotide, as discussed above, independent claims 1 and 16 have been amended to recite that "said first and said second block of RNA residues are about 3 nucleotides to about 20 nucleotides in length" and the "first block of DNA residues is about 5 nucleotides to about 60 nucleotides in length." The Examiner's concerns regarding the variability in length of the oligonucleotide have been addressed by this amendment.

II. The Examiner asserts that the identification of nucleotide mismatches in any and/or all target genes of interest that would convert these target genes to inactive forms is undue (Office Action mailed September 23, 2003, page 8, lines 10-16). The Examiner states that, "the target genes previously taught in the art (e.g., ALS, GFP) or in the instant disclosure (EPSPS or AHAS, GFP) have been extensively characterized and single point mutations of particular amino acid residues have been identified with these target genes, which, when obtained, convert them from herbicide sensitive to herbicide resistant genes," however, the Examiner concludes that the identification of other alterations in other target genes is undue experimentation. Contrary to this opinion and as previously made of record, *the art is replete with known alterations (including, for example, recessive mutations, dominate mutations, stop mutations, and frame shift alterations) that inactivate a variety of characterized nucleotide sequences*. Accordingly, one of skill in the art could readily identify an appropriate alteration that would inactivate a nucleotide sequence of interest.

It is further emphasized that alterations in various sequences of interest that are not involved in herbicide resistance are also are known in the art. For example, sequences that play roles in various metabolic pathways, developmental pathways, etc. have been characterized. In fact, the art routinely engages in genetic screens to allow for the identification and cloning of sequences of interest. As evidence, Applicants submit Lodish *et al.* (1995) *Molecular Cell*

Biology, third edition, 269-274 (Appendix A) that outlines the general process of genetic screening and the subsequent isolation of gene of interest.

The claims recite "inactivating" a nucleotide sequence of interest. As outlined above, any type of inactivating alteration could be made in the sequence. Again, designing such alterations are routine. Various recessive or dominate mutations could be introduced into the sequence of interest. In addition, the Examiner is reminded that introducing frame shift alterations or stop condons would also readily inactivate a sequence of interest. In summary, in view of the facts outlined above, contrary to the assertion in the Office Action, it is incorrect to conclude that, among the vast number of characterized sequences in the art, only AHAS, GFP, and EPSP have been characterized sufficiently for one of skill to design an inactivating alteration.

III. The Examiner maintains that the state of the art was unpredictable. Specifically, the Examiner states that the "specification teaches...that nucleotide conversions do not consistently reflect the mismatches anticipated by the DNA block sequences containing the nucleotide mismatch within the chimeric oligonucleotide." The Examiner therefore concludes that a method for inactivating a nucleotide sequence of interest using the claimed methods is unpredictable. Applicants respectfully disagree.

As previously made of record, the instant specification provides data demonstrating two independent target sequences within the endogenous maize AHAS sequence were modified in a site-specific fashion, thereby conferring resistance to either imidazolinone or sulfonylurea herbicides. Similarly, two independently inserted GFP transgenes were site-specifically modified *in vivo*. *In all cases, the modifications resulted in the expected/desired phenotypes.*

In fact, the instant specification teaches a conversion frequency of 100 fold greater than that arising from spontaneous mutation. This conversion frequency is high enough to allow for the successful identification/selection of a plant cell having the desired alteration. As the art routinely performs genetic screens for spontaneous mutation in plants for the identification of desirable phenotypes, alterations occurring at 100 fold higher frequency can be routinely identified by one of skill in the art. Accordingly, Applicant's continue to maintain that, contrary

to the Examiner's conclusions, the specification does not teach that the claimed methods are unpredictable.

IV. In summary, the Office Action has failed to provide either evidence for the unpredictability of the claimed methods or evidence demonstrating that undue experimentation is required to practice the claimed methods.

As previously made of record, Applicants have successfully identified accessible target sites in two independent PAT/GFP transgenes having distinct and independent chromosomal positions (see, example 2, page 27-28). Similarly, two different positions in the AHAS gene were also successfully targeted (see, example 2 and table 2 of the specification). In addition, the specification provides specific guidance for target sites in EPSPS, and moreover, provides general strategies for determining appropriate target sites in other genes. See, for example, page 11, lines 22-29 and page 22, lines 3-23 of the specification.

As made of record in the July 28, 2003 Amendment and Response, the results provided both in the instant application and in Kochevenko *et al.* (2003) *Plant Physiology 132*:174-184 and Beetham *et al.* (1999) *Proc. Natl. Acad. Sci. 96*:8874-8778, clearly establish that only routine experimentation is required to practice the claimed invention. In fact, Applicants provided evidence of the successful targeting of *7 independent genomic positions in plants.*

The Examiner is reminded that the Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation needed to practice the invention is not undue. *In re Wands*, 8 USPQ2d 1400 (Fed Cir 1988). Furthermore, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. *Id.* As the target sequence is known and the screening methods are adequately described in the specification, the synthesis and screening of chimeric oligonucleotides is nothing more than routine experimentation analogous to the hybridoma screening the Federal Circuit found acceptable in *In re Wands* (858 F.2d 731,8 USPQ 1400(Fed. Cir. 1988)). *See also Johns Hopkins University v. Cellpro*, 931 F. Supp. 303, 324 (D. Del. 1996), *aff'd in part, vacated*

in part, & remanded, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998) ("The specification need only enable one mode of making the claimed invention.").

In view of the comments and evidence present above, Applicants respectfully request that the rejection of claims 1-8, 13-22, and 27-29 under 35 U.S.C. § 112, first paragraph, be withdrawn.

CONCLUSIONS

The Examiner is respectfully requested to withdraw the rejections under 35 U.S.C. § 112, first and second paragraph, and allow claims 1-29. In any event, the Examiner is respectfully requested to withdraw finality of the Action issued September 23, 2003 and enter the above amendments for purposes of further prosecution. The amendments were not made earlier because the Applicant earnestly believes the specification is enabling for the breadth of the claims as originally drafted and the methods are sufficiently described in the claims. All the amendments made herein were made pursuant to suggestions made by the Examiner.

Accordingly, in view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Kelly J. Williamson

Kelly J. Williamson
Patent Agent
Registration No. 47,179